Palliative Care Rounds: Towards Evidence-Based Practice

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Depression in Terminally Ill Patients: Dilemmas in Diagnosis and Treatment

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Introduction

Psychiatric diagnoses are common in up to 50% of patients with incurable conditions.[1] The Canadian National Palliative Care Survey found that 13% of palliative care patients ($N = 381$) had a diagnosis of major depression. When patients with mild depression, dysthymia, and other depressive disorders were included, the total proportion rose to 44%.[2] Mitchell et al. conducted a recent meta-analysis of 94 psychiatric interview-based studies that assessed cancer patients for depressive disorders. The prevalence of major depressive disorder in both palliative and nonpalliative care settings was found to be 14%, rising to 24% when all forms of depressive illness (minor depression and dysthymia) were included.[3] However, differentiating depressive disorders from an appropriate grief reaction in the setting of a terminal illness may be difficult,[4,5] and underdetection and undertreatment of the psychological and psychiatric morbidity developed in terminally ill patients are common.[6]

Anhedonia, a lack of interest or pleasure in previously enjoyable activities, is a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criterion for depression, but it also could be attributed to decreased functional status because of the primary illness. It may be difficult to discern if the person is withdrawing from previously enjoyable activities because of depression or declining function and strength resulting from the terminal illness make the activities less enjoyable. Furthermore, many DSM-IV criteria commonly used to diagnose depression are related to somatic complaints (weight loss, fatigue, loss of appetite, and insomnia) that also are symptoms of terminally ill patients' underlying diagnoses and thus not very helpful in distinguishing depression from symptoms of their terminal illness.[7] Endicott[8] proposed that in the assessment of depression in cancer patients, somatic symptoms should be substituted (Table 1). Akechi et al.[9] compared the Endicott substitutions with DSM-IV criteria in 728 patients with cancer. Based on their assessment, the "fearfulness" and "brooding" items were suggestive of mild major depression, the "social withdrawal" item correlated with moderate severity of major depression, and the "cannot be cheered up" item indicated severe major depression.[9] Evidence of hopelessness, helplessness, worthlessness, guilt, and suicidal ideation may be better indicators of depression in terminally ill patients than neurovegetative symptoms.[4] Another significant problem in the terminally

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Table 1
Proposed Substitution of Somatic DSM-IV Criteria for Depression for Other Symptoms in Terminally Ill Patients (adapted per Endicott[8])

DSM-IV Criterion	Substituted for
Poor appetite/weight loss	Fearfulness or depressed appearance in body or face
Insomnia/hypersomnia	Social withdrawal or decreased talkativeness
Loss of energy/fatigue	Brooding, self-pity, and pessimism
Diminished concentration or slowed thinking	Cannot be cheered up, does not smile, no response to good news, or funny situations

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.*

ill population is patients' short life expectancy and the significant length of time needed (weeks) for commonly used antidepressants (i.e., selective serotonin reuptake inhibitor [SSRIs]) to take effect.

Case Description

Mr. G. is a 75-year-old, cognitively intact, divorced, retired salesman being seen in the palliative care clinic. He has been diagnosed with chronic obstructive pulmonary disease and Stage IV non-small cell lung cancer, with known adrenal metastases, and recent progression of his mediastinal lymphadenopathy despite second-line chemotherapy. Given his poor functional status (Eastern Cooperative Oncology Group Performance Status 3), he has no further treatment options according to his oncologist. His life expectancy is estimated to be less than six months. He reports that his worst symptoms are fatigue, loss of appetite, weight loss of 10 lbs. in the last month, and difficulty falling asleep and staying asleep. On examination, he has poor eye contact, does not smile, and appears sad. He is mildly short of breath with minimal exertion and has been on 2 L of oxygen at home for the last two years. He has pain from osteoarthritis in his back that is controlled with hydrocodone/acetaminophen 5/500 mg two to three times daily. Mr. G. used to be quite social and volunteered at a nursing home, playing piano for the residents. He also was playing poker and dominoes twice a week at a senior center. When asked about how his disease has affected his interests, he admits that over the last month, he has given up all these activities. He states, "I can't do anyone any good in the state I am in, doc" and "I don't want my friends to see me withering away." He lives alone, but since his illness, his ex-wife has been visiting him almost daily and helps him with cleaning and meal preparation. "I am grateful she is coming, but if she didn't, it would be ok—I would just die a bit faster because she always forces me to eat." They have a son and a daughter who live out of state.

You ask yourself the following questions:

1. Does Mr. G. suffer from clinical depression, or does he have an appropriate reaction to receiving/dealing with bad news ("grief reaction/sadness")?
2. If he does have depression, what is the evidence regarding best treatment options for depression in terminally ill patients?

Comment

Question 1

We performed a MEDLINE and Cochrane database search for peer-reviewed articles through June 2012. We conducted our search using the terms "terminally ill" or "seriously ill" or "palliative care" combined with "depression," and "screening" or "assessment." We included studies that described screening tools for depression that had been used in terminally ill patients. We included only studies that had data on sensitivity and specificity and had a comparison group to a gold standard (i.e., semistructured psychiatric interview using the Present State Examination or DSM-IV).

The search yielded 112 results, of which we excluded reviews, opinion articles, and letters. We also excluded pure prevalence studies and ultimately included 11 studies that were reviewed in detail.[10–20] Most studies were done in inpatients with advanced cancer. Thekkumpurath et al.[21] published a review article on screening for depression in palliative care that included eight of the identified studies. We

found several tools that have been validated for patients with advanced cancer. These patients were similar to our patient by diagnosis, except for the fact that most patients were studied in an inpatient setting. The most commonly used validated tools for advanced cancer patients are unidimensional screening instruments: 1) single-item ("Are you depressed?")[10,13,14,22,23] or 2) two-item interview ("Have you been bothered by feeling down, depressed, or hopeless?" and "Have you lost interest or pleasure in doing things?"),[10,15,16,22,23] and 3) a visual analogue scale for depressed mood;[10,14] and multidimensional screening instruments: 4) the Beck Depression Inventory-Short Form,[10] 5) the Hospital Anxiety and Depression Scale (HADS),[11,15,18–20] 6) the Mood Evaluation Questionnaire,[13] and 7) the Edinburgh Postnatal Depression Scale.[12,14] Although originally developed to measure postpartum depression, this last 10-item instrument has been validated in patients with advanced cancer (with a cut-off of 13, it had a sensitivity of 81% and specificity of 79%, $N = 100$).[12] It does not contain any somatic-type symptoms but does include items on guilt, thoughts of self-harm, and hopelessness. Lloyd-Williams et al.[17] developed a six-item version of this instrument that was validated against the Present State Examination and found to have a sensitivity of 72% and specificity of 83%, using a cut-off of 6, $N = 246$. Of note, in the Lloyd-Williams et al.[23] measurement, the single item ("Are you depressed?") was found to be less specific and sensitive than in other (U.S.) findings.

In 2011, European evidence-based guidelines were developed for the prevention, detection, diagnosis, assessment, and treatment of depression in patients receiving palliative care.[24] These guidelines supported regular screening, using either the single-item or two-item questions, the Edinburgh Postnatal Depression Scale or the HADS, which includes 14 items, seven for anxiety and seven for depression.[9] A Delphi method was used to elicit expert opinion on which screening instrument for depression in palliative care patients should be recommended.[25] Opinions varied widely but included the above tools plus the recommendation for "routine informal asking" about mood. Thus, screening likely will be balanced by need for brevity of assessment, familiarity with the instrument, and individual preference. Screening should lead to further in-depth assessment.

For diagnosis of a depressive disorder, the guidelines recommended both the Hamilton Depression Rating Scale and the Beck Depression Inventory, both of which have been independently validated in cancer patients and palliative care populations.[24] Additionally, the authors of the guidelines provided features of sadness that help distinguish it from depression. Some of these characteristics include: 1) ability to feel intimately connected with others, 2) ability to enjoy happy moments, 3) occurs in waves, 4) sense of self-worth, and 5) will to live.[24]

Question 2

We again performed a MEDLINE and Cochrane database search for peer-reviewed articles through June 2012. We conducted our search using the terms "terminally ill" or "seriously ill" or "palliative care" combined with "depression," and "treatment." Additionally, we combined the terms "antidepressant" or "psychotherapy" or "psychostimulant" with the terms "terminally ill" or "seriously ill" or "palliative care." We evaluated the studies based on their quality, that is, did the investigators have a control group? If a control group was used, was the study blinded? Randomized? Placebo-controlled? How was clinical response or failure evaluated? If the treatment was nonpharmacologic, what placebo treatment, if any, did the control group receive? We included studies evaluating both pharmacologic and nonpharmacologic therapies. All authors met and reached a consensus about which studies were to be included. Hand searches supplemented the database search through examination of the references in identified studies and related studies.

Our search regarding the best treatment options for depression in terminally ill patients yielded 296 results. After restricting results to randomized controlled trials, 66 studies remained, which were further evaluated. For psychostimulants, we reviewed any type of study as there was only one randomized trial. Most trials were for nonpharmacologic treatments.

Nonpharmacologic Therapies. Psychosocial interventions have been mostly conducted in cancer patients. A Cochrane meta-analysis on

psychotherapy for depression among patients with incurable cancer found that psychotherapy was associated with a significant decrease in depression scores; the standardized mean difference of change between the baseline and immediate post-treatment scores was −0.44 (meta-analysis included $N = 292$ patients in the psychotherapy arms and $N = 225$ patients in the control arm).[26] The quality of all these trials was poor to fair. Additionally, none of the patients had clinically diagnosed depression, and efficacy was evaluated by change (decrease) in depressive symptom scores. Psychotherapies examined included supportive psychotherapy (four studies), cognitive behavioral therapy (CBT) (one study), and problem-solving therapy (one study). A recent pilot study of individual meaning-centered psychotherapy for patients with advanced Stage III or IV cancer (again, without clinically diagnosed depression) did not show any improvement in depressive scores compared with a comparison group receiving therapeutic massage.[27]

Dignity therapy, a form of individualized short-term psychotherapy, was examined in a large, multicountry, randomized controlled trial for terminally ill inpatients or outpatients who received hospice care.[28] One hundred sixty-five patients were randomly assigned to dignity therapy in addition to hospice care, 140 patients were assigned to client-centered care plus hospice care, and 136 patients were assigned to standard hospice care alone. Outcome measures were reductions in dimensions of distress; the HADS was used to assess the severity of depressive symptoms. Although dignity therapy had beneficial effects, this study could not show unequivocal improvement in depression, desire for death, or suicidality.[28]

Other interventions have used collaborative care models of care delivery[29–31] and novel technology[32] for cancer patients, but all excluded patients with a life expectancy of less than six months.

One recent pilot study compared CBT with aromatherapy massage, randomly recruiting 39 depressed outpatients with cancer.[33] Patients received up to eight weekly sessions of either CBT or aromatherapy massage. Investigators found significant improvement in depression scores for both interventions; between-group comparison showed a nonsignificant trend toward greater improvement with CBT. Two other trials, one in cancer patients of any stage ($N = 288$)[34] and one in patients with advanced cancer ($N = 42$),[35] evaluated aromatherapy massage. The larger study assigned patients randomly to either aromatherapy massage or usual supportive care only. Whereas investigators found a significant reduction in depression scores for aromatherapy patients at two weeks after intervention, no difference remained at six weeks.[34] Soden et al.[35] found no benefit of aromatherapy massage over massage therapy, but patients had statistically significant reductions in depressive symptoms for both therapies compared with no intervention.

Psychopharmacotherapy. Many antidepressants have been shown to be effective in depressed primary care patients[36] and in depressed patients with at least one chronic illness.[37,38] Pharmacotherapy of depression for patients with limited life expectancy is challenging because the most commonly used antidepressants, that is, SSRIs, take approximately four weeks to show benefits.[39] Evidence in support of antidepressant pharmacotherapy in terminally ill patients is mostly of low quality. The few placebo-controlled trials conducted in cancer patients have yielded mixed results.[40–46]

Only two of these placebo-controlled trials evaluated an antidepressant specifically in patients with advanced cancer, which was defined as having a life expectancy between 3 and 24 months.[43,44] Drugs examined were the tetracyclic mianserin,[40,41] fluoxetine,[41–44] the tricyclic desipramine,[44] and paroxetine.[45,46]

Recent European evidence-based guidelines (and in the absence of evidence, expert opinion) recommend considering antidepressant therapy with an SSRI and psychological therapy, in particular CBT, for the treatment of depression in palliative care.[24] A meta-analysis by the same group assessed efficacy of antidepressants vs. placebo in patients receiving palliative care.[47] They found antidepressants to be more efficacious than placebo, and efficacy increased over time. The number needed-to-treat decreased from nine at four to five weeks to six at six to eight weeks and to five at 9–18 weeks. Both main classes of antidepressant (tricyclic antidepressants and SSRIs) were effective in treating depression in palliative care patients.

Although treating depression is important, it is worth emphasizing that it also is important

not to treat patients unnecessarily who are not depressed. A randomized, double-blind, placebo-controlled trial showed that among advanced cancer patients without major depression, the ones assigned to sertraline 50 mg had no benefit over placebo in any of the outcome measures.[48] The problem with the majority of the studies is that often patients with any "depressive symptoms" were treated, not necessarily just patients who met criteria for major depression. Terminally ill patients should not be exposed to potential adverse effects of an antidepressant if the treatment indication is not clear.

Psychostimulants, used in oncology and palliative care settings to treat fatigue, also may have a role in the management of depression because of their rapid onset of action. However, most studies were open-label small trials with $N < 60$[49–52] and of short duration (less than two weeks). Macleod[51] found that among patients who died within six weeks, only 7% responded, vs. 46% among the patients who lived longer than six weeks. Only one small study was randomized, double-blind, and placebo-controlled: Among 30 hospice patients treated for 14 days, depressed patients achieved a significant reduction in three different scores for depressed mood; placebo patients had less changes in depression scores than the treatment group, but effects were inconsistent between the three assessment tools.[53] In all studies, the treatment seemed to be well tolerated.

Conclusion

Several brief screening tools have been used for terminally ill patients with advanced cancer and may be used effectively in screening for depression in these patients. However, because most were validated in patients with advanced cancer, it is less clear if they would detect depression as well in other terminally ill patients with noncancer diagnoses. There is only weak evidence that screening improves outcomes. Similar to our inability to define a "best screening instrument" to assess for depression, we found there also is no "best antidepressant" to be recommended, and good quality comparative effectiveness studies are lacking. Terminally ill patients are a very heterogeneous group with different underlying illnesses; most studies have been done in cancer patients, and results may not necessarily be applicable to patients with other terminal illnesses. Additionally, many studies excluded patients with a life expectancy of less than six months. However, a variety of effective treatment options exist and depression should be treated without delay because of its enormous impact on quality of life. Physicians have been choosing certain antidepressants over others empirically, based on their expected side effect profile and potential other effects on symptoms, and familiarity with the drug.

Although research in screening, diagnosing, and treating depression in terminally ill patients has made advances in the last decade, efforts should be made to include more patients with noncancer diagnoses in studies. Despite growing evidence for the validity of the screening and diagnostic tools, the overlap of somatic symptoms, prevalence of delirium, medication effects, and anxiety continue to pose challenges to accurately diagnose depression in terminally ill patients. Additionally, more research using nonpharmacologic treatments is encouraging. Although psychotherapeutic approaches can be impeded in patients with compromised or fluctuating cognition, the growing literature for psychotherapeutic interventions is promising and may provide faster results more effectively.

Case Outcome

Mr. G. endorsed depression on both the two-item questionnaire and the HADS (we used this tool as it also has been tested in outpatients with advanced cancer, similar to our patient),[17] and treatment with mirtazapine 15 mg at bedtime was begun and chosen for its sedative properties. He also began meeting with a psychologist weekly for supportive psychotherapy. His insomnia improved first and after three to four weeks his mood began to lift considerably. Unfortunately, social withdrawal did not change very much because the patient continued to get weaker and his functional status deteriorated so that he was unable to return to his previous activities. However, he expressed more enjoyment from visits from friends and co-volunteers from the senior facility where he had previously volunteered

and his ex-wife. After eight weeks, he became completely bedbound and was admitted to a Veterans Administration inpatient palliative care unit where he passed away three weeks later.

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References

1. Derogatis LR, Westlake SK. The prevalence of psychiatric disorders among cancer patients. JAMA 1983;249:751–757.

2. Wilson KG, Chochinov HM, Skirko MG, et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage 2007;33:118–129.

3. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12: 160–174.

4. Block SD. Assessing and managing depression in the terminally ill patient. ACP-ASIM End-of-Life Care Consensus Panel. American College of Physicians–American Society of Internal Medicine. Ann Intern Med 2000;132:209–218.

5. Periyakoil VS, Kraemer HC, Noda A, et al. The development and initial validation of the Terminally Ill Grief or Depression Scale (TIGDS). Int J Methods Psychiatr Res 2005;14:202–212.

6. Stiefel F, Die-Trill M, Berney A, Olarte JM, Razavi A. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Support Care Cancer 2001;9:477–488.

7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.

8. Endicott J. Measurement of depression in patients with cancer. Cancer 1984;53:2243–2248.

9. Akechi T, Ietsugu T, Sukigara M, et al. Symptom indicator of severity of depression in cancer patients: a comparison of the DSM-IV criteria with alternative diagnostic criteria. Gen Hosp Psychiatry 2009;31:223–232.

10. Chochinov HM, Wilson KG, Enns M, Lander S. "Are you depressed?" Screening for depression in the terminally ill. Am J Psychiatry 1997;154: 674–676.

11. Le Fevre P, Devereux J, Smith S, Lawrie SM, Cornbleet M. Screening for psychiatric illness in the palliative care inpatient setting: a comparison between the Hospital Anxiety and Depression Scale and the General Health Questionnaire-12. Palliat Med 1999;13:399–407.

12. Lloyd-Williams M, Friedman T, Rudd N. Criterion validation of the Edinburgh Postnatal Depression Scale as a screening tool for depression in patients with advanced metastatic cancer. J Pain Symptom Manage 2000;20:259–265.

13. Meyer HA, Sinnott C, Seed PT. Depressive symptoms in advanced cancer. Part 1. Assessing depression: the Mood Evaluation Questionnaire. Palliat Med 2003;17:596–603.

14. Lloyd-Williams M, Dennis M, Taylor F. A prospective study to compare three depression screening tools in patients who are terminally ill. Gen Hosp Psychiatry 2004;26:384–389.

15. Akechi T, Okuyama T, Sugawara Y, et al. Screening for depression in terminally ill cancer patients in Japan. J Pain Symptom Manage 2006;31: 5–12.

16. Payne A, Barry S, Creedon B, et al. Sensitivity and specificity of a two-question screening tool for depression in a specialist palliative care unit. Palliat Med 2007;21:193–198.

17. Lloyd-Williams M, Shiels C, Dowrick C. The development of the Brief Edinburgh Depression Scale (BEDS) to screen for depression in patients with advanced cancer. J Affect Disord 2007;99:259–264.

18. Olden M, Rosenfeld B, Pessin H, Breitbart W. Measuring depression at the end of life: is the Hamilton Depression Rating Scale a valid instrument? Assessment 2009;16:43–54.

19. Walker J, Postma K, McHugh GS, et al. Performance of the Hospital Anxiety and Depression Scale as a screening tool for major depressive disorder in cancer patients. J Psychosom Res 2007;63:83–91.

20. Lloyd-Williams M, Friedman T, Rudd N. An analysis of the validity of the Hospital Anxiety and Depression scale as a screening tool in patients with advanced metastatic cancer. J Pain Symptom Manage 2001;22:990–996.

21. Thekkumpurath P, Venkateswaran C, Kumar M, Bennett MI. Screening for psychological distress in palliative care: a systematic review. J Pain Symptom Manage 2008;36:520–528.

22. Mitchell AJ. Are one or two simple questions sufficient to detect depression in cancer and palliative care? A Bayesian meta-analysis. Br J Cancer 2008;98:1934–1943.

23. Lloyd-Williams M, Dennis M, Taylor F, Baker I. Is asking patients in palliative care, "Are you depressed?" appropriate? Prospective study. BMJ 2003;327:372–373.

24. Rayner L, Price A, Hotopf M, Higginson IJ. The development of evidence-based European guidelines on the management of depression in palliative cancer care. Eur J Cancer 2011;47:702–712.

25. Rayner L, Price A, Hotopf M, Higginson IJ. Expert opinion on detecting and treating depression in palliative care: a Delphi study. BMC Palliat Care 2011;10:10.

26. Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. Cochrane Database Syst Rev 2008;2:CD005537.

27. Breitbart W, Poppito S, Rosenfeld B, et al. Pilot randomized controlled trial of individual meaning-centered psychotherapy for patients with advanced cancer. J Clin Oncol 2012;30:1304–1309.

28. Chochinov HM, Kristjanson LJ, Breitbart W, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. Lancet Oncol 2011;12: 753–762.

29. Ell K, Xie B, Quon B, et al. Randomized controlled trial of collaborative care management of depression among low-income patients with cancer. J Clin Oncol 2008;26:4488–4496.

30. Strong V, Waters R, Hibberd C, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet 2008;372: 40–48.

31. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 2009; 302:741–749.

32. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer. JAMA 2010;304:163–171.

33. Serfaty M, Wilkinson S, Freeman C, Mannix K, King M. The ToT study: helping with Touch or Talk (ToT): a pilot randomised controlled trial to examine the clinical effectiveness of aromatherapy massage versus cognitive behaviour therapy for emotional distress in patients in cancer/palliative care. Psychooncology 2012;21:563–569.

34. Wilkinson SM, Love SB, Westcombe AM, et al. Effectiveness of aromatherapy massage in the management of anxiety and depression in patients with cancer: a multicenter randomized controlled trial. J Clin Oncol 2007;25:532–539.

35. Soden K, Vincent K, Craske S, Lucas C, Ashley S. A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 2004;18:87–92.

36. Arroll B, Elley CR, Fishman T, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev 2009;3:CD007954.

37. Taylor D, Meader N, Bird V, et al. Pharmacological interventions for people with depression and chronic physical health problems: systematic review and meta-analyses of safety and efficacy. Br J Psychiatry 2011;198:179–188.

38. Rayner L, Price A, Evans A, et al. Antidepressants for depression in physically ill people. Cochrane Database Syst Rev 2010;3:CD007503.

39. Gelenberg AJ, Chesen CL. How fast are antidepressants? J Clin Psychiatry 2000;61:712–721.

40. Costa D, Mogos I, Toma T. Efficacy and safety of mianserin in the treatment of depression of women with cancer. Acta Psychiatr Scand 1985; 72(Suppl 30):85–92.

41. van Heeringen K, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. Br J Psychiatry 1996;169:440–443.

42. Razavi D, Allilaire JF, Smith M, et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand 1996;94: 205–210.

43. Fisch MJ, Loehrer PJ, Kristeller J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group. J Clin Oncol 2003;21:1937–1943.

44. Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. Psychooncology 1998;7:291–300.

45. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89: 243–249.

46. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized double-blind trial from the University of Rochester Cancer Centre Community Clinical Oncology Program. J Clin Oncol 2003;21: 4635–4641.

47. Rayner L, Price A, Evans A, et al. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis. Palliat Med 2011;25:36–51.

48. Stockler MR, O'Connell R, Nowak AK, et al. Zoloft's Effects on Symptoms and Survival Time Trial Group. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. Lancet Oncol 2007;8: 603–612. Erratum in Lancet Oncol 2007;8:574.

49. Fernandez F, Adams F, Holmes VF, Levy JK, Neidhart M. Methylphenidate for depressive disorders in cancer patients. An alternative to standard antidepressants. Psychosomatics 1987;28:455–461.

50. Olin J, Masand P. Psychostimulants for depression in hospitalized cancer patients. Psychosomatics 1996;37:57–62.

51. Macleod AD. Methylphenidate in terminal depression. J Pain Symptom Manage 1998;16: 193–198.

52. Homsi J, Nelson KA, Sarhill N, et al. A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care 2001;18: 403–407.

53. Kerr CW, Drake J, Milch RA, et al. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage 2012;43:68–77.